

We claim:

1. A modified GDF-8 propeptide comprising a GDF-8 propeptide, wherein the modified GDF-8 propeptide has an increased in vivo or in vitro half-life relative to a corresponding unmodified GDF-8 propeptide.

1. The modified GDF-8 propeptide of claim 1, wherein the GDF-8 propeptide comprises an amino acid sequence that is at least 75% identical to SEQ ID NO:5.

3. The modified GDF-8 propeptide of claim 1, wherein the GDF-8 propeptide is identical to SEQ ID NO:5.

4. The modified GDF-8 propeptide of claim 1, wherein the GDF-8 propeptide contains an inactivated proteolytic cleavage site.

5. The modified GDF-8 propeptide of claim 4, wherein the proteolytic cleavage site is inactivated by a mutation to said site.

6. The modified GDF-8 propeptide of claim 1, wherein the modified GDF-8 propeptide further comprises a stabilizer portion fused to the GDF-8 propeptide.

7. The modified GDF-8 propeptide of claim 6, wherein the stabilizer portion comprises an Fc region of an IgG molecule.

8. The modified GDF-8 propeptide of claim 7, wherein the IgG molecule

is IgG1 or IgG4, or derivatives thereof.

9. The modified GDF-8 propeptide of claim 7, wherein the IgG molecule is IgG1.
10. The modified GDF-8 propeptide of claim 7, wherein the amino acid sequence of the IgG molecule is at least 75% identical to SEQ ID NO:15.
11. The modified GDF-8 propeptide of claim 7, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:15.
12. The modified GDF-8 propeptide of claim 7, wherein the amino acid sequence of the IgG molecule is at least 75% identical to SEQ ID NO:16.
13. The modified GDF-8 propeptide of claim 7, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:16.
14. The modified GDF-8 propeptide of claim 6, wherein the GDF-8 propeptide is fused to the Fc region of the IgG molecule via a linker peptide.
15. The modified GDF-8 propeptide of claim 1, wherein the modified GDF-8 propeptide has an altered glycosylation site.
16. The modified GDF-8 propeptide of claim 1, wherein the modified GDF-8 propeptide comprises at least one carbohydrate moiety.

17. The modified GDF-8 propeptide of claim 6, wherein the stabilizer portion comprises albumin or a derivative of albumin.
18. The modified GDF-8 propeptide of claim 6, wherein the stabilizer portion comprises a nonproteinaceous polymer.
19. The modified GDF-8 propeptide of claim 1, wherein the modified GDF-8 propeptide further comprises one or more point mutations, wherein said point mutation inhibits proteolytic cleavage.
20. The modified GDF-8 propeptide of claim 1, wherein the modified GDF-8 propeptide further comprises a purification tag.
21. A nucleic acid encoding a modified GDF-8 propeptide wherein said modified GDF-8 propeptide has an increased in vivo or in vitro half life as relative to a corresponding unmodified GDF-8 propeptide.
22. The nucleic acid of claim 21, comprising at least 20 contiguous nucleotides as set forth in SEQ ID NO: 2.
23. The nucleic acid of claim 21, comprising at least 20 contiguous nucleotides as set forth in SEQ ID NO: 6.
24. The nucleic acid of claim 21, comprising at least 50 contiguous nucleotides as set forth in SEQ ID NO: 2.
25. The nucleic acid of claim 21, comprising at least 50 contiguous nucleotides as set forth in SEQ ID NO: 6.

26. The nucleic acid of claim 21 further comprising a nucleic acid encoding a stabilizer protein.
27. The nucleic acid of claim 26, wherein the stabilizer portion encodes an IgG protein.
28. The nucleic acid of claim 26, wherein the stabilizer portion encodes albumin or an albumin derivative.
29. The nucleic acid of claim 21, wherein the nucleic acid encodes a modified GDF-8 propeptide with an altered glycosylation site.
30. The nucleic acid of claim 21, wherein the nucleic acid encodes a modified GDF-8 propeptide with an altered carbohydrate moiety.
31. A pharmaceutical composition comprising the modified GDF-8 propeptide of claim 1 and a pharmaceutically acceptable excipient.
32. A pharmaceutical composition comprising the nucleic acid of claim 21 and a pharmaceutically acceptable carrier or vector.
33. The method of making a modified GDF-8 propeptide comprising:
 - (a) preparing a cDNA molecule encoding the GDF-8 propeptide, wherein the proteolytic cleavage site is modified;
 - (b) preparing a cDNA molecule encoding the Fc region of the IgG molecule; and

(c) fusing the cDNA molecules from steps (a) and (b) to produce a modified GDF-8 propeptide.

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34. The method of claim 33, further comprising preparing a double-stranded oligonucleotide encoding a linker peptide and fusing the cDNA molecules from steps (a) and (b) to either end of the double-stranded oligonucleotide encoding the linker peptide.
35. The method of claim 33, wherein the linker peptide comprises the amino acid sequence consisting of GSGS.
36. A recombinant cell comprising a nucleic acid encoding a modified GDF-8 propeptide.
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37. The recombinant cell of claim 36, wherein said nucleic acid comprises a nucleic acid sequence encoding a stabilizer portion.
38. A method of treating a patient suffering from a medical disorder or disease comprising: administering a therapeutically effective amount of a modified GDF-8 propeptide and a pharmaceutically acceptable excipient to said patient, wherein the modified GDF-8 propeptide has an increased in vivo or in vitro half life relative to a corresponding unmodified GDF-8 propeptide.
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39. The method of claim 38, wherein the GDF-8 propeptide comprises an amino acid sequence that is at least 75% identical to SEQ ID NO:5.
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40. The method of claim 38, wherein the GDF-8 propeptide is SEQ ID NO:5.
41. The method of claim 38, wherein the GDF-8 propeptide contains a mutation in one or more proteolytic cleavage sites.
42. The method of claim 38, wherein the modified GDF-8 propeptide further comprises an Fc region of an IgG molecule.
43. The method of claim 42, wherein the IgG molecule is IgG1 or IgG4, or a derivative thereof.
44. The method of claim 42, wherein the IgG molecule is IgG1.
45. The method of claim 42, wherein the IgG molecule is at least 75% identical to SEQ ID NO:15.
46. The method of claim 42, wherein the Fc region of an IgG molecule is identical to SEQ ID NO:15.
47. The method of claim 42, wherein the IgG molecule is at least 75% identical to SEQ ID NO:16.
48. The method of claim 42, wherein the Fc region of an IgG molecule is identical to SEQ ID NO:16.
49. The method of claim 38, wherein the modified GDF-8 propeptide has an altered glycosylation site.

50. The method of claim 38, wherein the modified GDF-8 propeptide comprises at least one carbohydrate moiety.
51. The method of claim 38, wherein the modified GDF-8 propeptide further comprises albumin or a derivative of albumin.
52. The method of claim 38, wherein the modified GDF-8 propeptide further comprises a nonproteinaceous polymer.
53. The method of claim 38, wherein the medical disorder is a muscular disorder, neuromuscular disorder, metabolic disorder or bone degenerative disorder.
54. The method of claim 38, wherein the medical disorder is a muscular or neuromuscular disorder.
55. The method of claim 38, wherein the medical disorder is a metabolic disorder.
56. The method of claim 38, wherein the medical disorder is amyotrophic lateral sclerosis, muscular dystrophy, muscle atrophy, congestive obstructive pulmonary disease, muscle wasting syndrome, sarcopenia, or cachexia.
57. The method of claim 38, wherein the medical disorder is amyotrophic lateral sclerosis or muscular dystrophy.

58. The method of claim 38, wherein the medical disorder is obesity, adipose tissue disorder, noninsulin-dependent diabetes mellitus, or type 2 diabetes.
59. The method of claim 38, wherein the medical disorder is osteoporosis.
60. A modified BMP-11 propeptide comprising a BMP-11 propeptide, wherein the modified BMP-11 propeptide has an increased in vivo or in vitro half-life relative to a corresponding unmodified BMP-11 propeptide.
61. The modified BMP-11 propeptide of claim 60, wherein the BMP-11 propeptide comprises an amino acid sequence that is at least 75% identical to SEQ ID NO: 11.
62. The modified BMP-11 propeptide of claim 60, wherein the BMP-11 propeptide is identical to SEQ ID NO: 11.
63. The modified BMP-11 propeptide of claim 60, wherein the BMP-11 propeptide contains an inactivated proteolytic cleavage site.
64. The modified BMP-11 propeptide of claim 62, wherein the proteolytic cleavage site is inactivated by a mutation to said site.
65. The modified BMP-11 propeptide of claim 60, wherein the modified BMP-11 propeptide further comprises a stabilizer portion fused to the BMP-11 propeptide.

66. The modified BMP-11 propeptide of claim 65, wherein the stabilizer portion comprises an Fc region of an IgG molecule.
67. The modified BMP-11 propeptide of claim 66, wherein the IgG molecule is IgG1 or IgG4, or derivatives thereof.
- 5 68. The modified BMP-11 propeptide of claim 66, wherein the IgG molecule is IgG1.
69. The modified BMP-11 propeptide of claim 66, wherein the amino acid sequence of the IgG molecule is at least 75% identical to SEQ ID NO:15.
- 10 70. The modified BMP-11 propeptide of claim 66, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:15.
71. The modified BMP-11 propeptide of claim 66, wherein the amino acid sequence of the IgG molecule is at least 75% identical to SEQ ID NO:16.
- 15 72. The modified BMP-11 propeptide of claim 66, wherein the amino acid sequence of the IgG molecule is SEQ ID NO:16.
73. The modified BMP-11 propeptide of claim 65, wherein the BMP-11 propeptide is fused to the Fc region of the IgG molecule via a linker peptide.

74. The modified BMP-11 propeptide of claim 60, wherein the modified BMP-11 propeptide has an altered glycosylation site.
75. The modified BMP-11 propeptide of claim 60, wherein the modified BMP-11 propeptide comprises at least one carbohydrate moiety.
76. The modified BMP-11 propeptide of claim 65, wherein the stabilizer portion comprises albumin or a derivative of albumin.
77. The modified BMP-11 propeptide of claim 65, wherein the stabilizer portion comprises a nonproteinaceous polymer.
78. The modified BMP-11 propeptide of claim 60, wherein the modified BMP-11 propeptide further comprises one or more point mutations, wherein said point mutation inhibits proteolytic cleavage.
79. The modified BMP-11 propeptide of claim 60, wherein the modified BMP-11 propeptide further comprises a purification tag.
80. A nucleic acid encoding a modified BMP-11 propeptide wherein said modified BMP-11 propeptide has an increased in vivo or in vitro half life as relative to a corresponding unmodified BMP-11 propeptide.
81. The nucleic acid of claim 80, comprising at least 20 contiguous nucleotides as set forth in SEQ ID NO: 8.
82. The nucleic acid of claim 80 comprising at least 20 contiguous nucleotides as set forth in SEQ ID NO: 12.

83. The nucleic acid of claim 80, comprising at least 50 contiguous nucleotides as set forth in SEQ ID NO: 8.
84. The nucleic acid of claim 80, comprising at least 50 contiguous nucleotides as set forth in SEQ ID NO: 12.
85. The nucleic acid of claim 80 further comprising a nucleic acid encoding a stabilizer portion.
86. The nucleic acid of claim 85, wherein the stabilizer portion encodes an IgG protein.
87. The nucleic acid of claim 85, wherein the stabilizer portion encodes albumin or an albumin derivative.
88. The nucleic acid of claim 80 wherein the nucleic acid encodes a modified BMP-11 propeptide with an altered glycosylation site.
89. The nucleic acid of claim 80 wherein the nucleic acid encodes a modified BMP-11 propeptide with an altered carbohydrate moiety.
90. A pharmaceutical composition comprising the modified BMP-11 propeptide of claim 61 and a pharmaceutically acceptable excipient.
91. A pharmaceutical composition comprising the nucleic acid of claim 80 and a pharmaceutically acceptable carrier or vector.

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92. The method of making a modified BMP-11 propeptide comprising:
- (a) preparing a cDNA molecule encoding the BMP-11 propeptide, wherein the proteolytic cleavage site is modified;
 - (b) preparing a cDNA molecule encoding the Fc region of the IgG molecule; and
 - (c) fusing the cDNA molecules from steps (a) and (b) to produce a modified BMP-11 propeptide.
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93. The method of claim 92, further comprising preparing a double-stranded oligonucleotide encoding a linker peptide and fusing the cDNA molecules from steps (a) and (b) to either end of the double-stranded oligonucleotide encoding the linker peptide.
94. The method of claim 92, wherein the linker peptide comprises the amino acid sequence consisting of GSGS.
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95. A recombinant cell comprising a nucleic acid encoding a modified BMP-11 propeptide.
96. The recombinant cell of claim 95 wherein said nucleic acid comprises a nucleic acid sequence encoding a stabilizer portion.
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97. A method of treating a patient suffering from a medical disorder or disease comprising: administering a therapeutically effective amount of a modified BMP-11 propeptide and a pharmaceutically acceptable excipient to said patient, wherein the modified BMP-11 propeptide has an increased in vivo or in vitro half life relative to a corresponding unmodified BMP-11 propeptide.

98. The method of claim 97, wherein the BMP-11 propeptide comprises an amino acid sequence that is at least 75% identical to SEQ ID NO:11.

99. The method of claim 97, wherein the BMP-11 propeptide is SEQ ID NO:11.

100. The method of claim 97, wherein the BMP-11 propeptide contains a mutation in one or more proteolytic cleavage sites.

101. The method of claim 97, wherein the modified BMP-11 propeptide further comprises an Fc region of an IgG molecule.

102. The method of claim 101, wherein the IgG molecule is IgG1 or IgG4, or a derivative thereof.

103. The method of claim 101, wherein the IgG molecule is IgG1.

104. The method of claim 101, wherein the IgG molecule is at least 75% identical to SEQ ID NO:15.

105. The method of claim 101, wherein the Fc region of an IgG molecule is identical to SEQ ID NO:15

106. The method of claim 101, wherein the IgG molecule is at least 75% identical to SEQ ID NO:16.

107. The method of claim 101, wherein the Fc region of an IgG molecule is identical to SEQ ID NO:16.

108. The method of claim 97, wherein the modified BMP-11 propeptide has an altered glycosylation site.
109. The method of claim 97, wherein the modified BMP-11 propeptide comprises at least one carbohydrate moiety.
110. The method of claim 97, wherein the modified BMP-11 propeptide further comprises albumin or a derivative of albumin.
111. The method of claim 97, wherein the modified BMP-11 propeptide further comprises a nonproteinaceous polymer.
112. The method of claim 97, wherein the medical disorder is a muscular disorder, neuromuscular disorder, metabolic disorder or bone degenerative disorder.
113. The method of claim 97, wherein the medical disorder is a muscular or neuromuscular disorder.
114. The method of claim 97, wherein the medical disorder is a metabolic disorder.
115. The method of claim 97, wherein the medical disorder is amyotrophic lateral sclerosis, muscular dystrophy, muscle atrophy, congestive obstructive pulmonary disease, muscle wasting syndrome, sarcopenia, or cachexia.

116. The method of claim 97, wherein the medical disorder is amyotrophic lateral sclerosis or muscular dystrophy.

117. The method of claim 97, wherein the medical disorder is obesity, adipose tissue disorder, noninsulin-dependent diabetes mellitus, or type 2 diabetes.

118. The method of claim 97, wherein the medical disorder is osteoporosis.